Jordan, Elke 2002

Dr. Elke Jordan Oral History

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National Human Genome Research Institute (NHGRI)

Interview #1 with Elke Jordan

Conducted on October 23, 2002, by Jennifer Rogers

JR: To start, let's discuss your education and career before NIH. Has genetics always been your primary field of study?

EJ: My primary interest, yes. My Ph.D. is in biochemistry, but I was always interested in the genetic aspects of that. At that time it was called biochemical genetics. And then soon thereafter, the term molecular biology emerged.

JR: When would you say that term came into vogue?

EJ: Molecular biology? That's a good question. In the sixties.

JR: Where did you receive your Ph.D.?

EJ: Johns Hopkins.

JR: What was the focus of your graduate work?

EJ: I worked on the metabolism of galactose in bacteria, and how it's regulated by genes.

JR: Did you work anywhere in that field before you came to NIH?

EJ: I worked at several places, alternating between galactose metabolism and genetic questions of bacteriophage lambda, which is related to galactose metabolism. Bacteriophage lambda can pick up galactose genes from one bacterial cell and transfer them to another bacterium. There was always an interconnection between those fields, even though they don't sound related on the surface, and I went back and forth between galactose and lambda in my research.

JR: How did you come to NIH?

EJ: Circuitously. I was working in Berkeley, and I had reached the decision that I needed to get out of laboratory work, that I needed to do something else. I looked at various possibilities, none of which really panned out. But there was a program at NIH at the time called the Grants Associates Program, which advertised for applicants in *Science* magazine. It sounded like something that really fit my situation, because it was a program to take laboratory researchers and train them in administration and management in preparation for taking jobs in the extramural programs of NIH. So I got into that program, and here I am. Been there ever since. That was in 1972.

JR: Did you start in the National Institute of General Medical Sciences [NIGMS]?

EJ: No, I actually started in the Cancer Institute and worked for a while in the virus cancer program, which is now defunct.

JR: That program is no longer around?

EJ: It no longer exists, no. At the time there was great enthusiasm for finding viruses that caused cancer in humans. Even though there are viruses associated with cancer in humans, as we know now, it's much more complex than was envisioned at the time. It isn't just find the virus and that's the sole cause. It's a multifactorial kind of cause, and the viruses that they were most after, the RNA viruses, really haven't been shown to be directly involved to that extent. So the program gradually died out. But I worked in it for a while, and then I moved on to NIGMS.

JR: Did NIGMS already have its Genetics Program when you moved there?

EJ: Yes. I went to the Genetics Program [Branch], and shortly after, I became deputy director of that program. Then I moved on to become associate director of the Institute for Program Activities, which was a position from which I coordinated all the programs and handled a lot of the management aspects.

JR: What was the focus of the NIGMS Genetics Program? From what I understand, much of the genetic research at NIH prior to the Genome Center [National Center for Human Genome Research] was within NIGMS. Is that correct?

EJ: A lot of the basic genetics research, yes. The program is very broad. It focused then, and I think now, mostly on model systems. Most of the human genetics is really in the other institutes and always has been. So there's a lot of work on *Drosophila,* mouse, bacteria, viruses, simple organisms, etcetera.

JR: So the human genetic research was really diffused throughout the rest of the institutes?

EJ: Yes.

JR: When you were at NIGMS you were involved in the creation of GenBank, correct?

EJ: Yes. That was one of the things that happened during that period. DNA sequencing, even though it was very slow at that time, was still coming into vogue, and a lot of sequence was being produced. Probably no more than could be done in a few minutes nowadays, but still, it was impossible to keep track of without computers. Some visionary folks foresaw that it would be necessary to collect all of the sequence data centrally so that it would be conveniently available for people to do research. Others felt they would rather have it collected on their own personal computers, and that having a central, national kind of database was not necessary. This was the era before the desktop computer was very powerful, and it was hard to foresee how computers and DNA sequencing would evolve. But the people who were pushing for the central database were clearly right. So there were lots of meetings, discussions, and controversy, as the NIGMS leadership was trying to decide how to respond to this little crisis. Finally they decided to organize a consortium of groups to fund such a centralized database. We had several NIH institutes and other agencies all chipping in a little money to get this started. That's how GenBank began, and it was managed as a contract from NIGMS. For some time the actual work was done at Los Alamos National Laboratory. There was a lot of community dissatisfaction with how GenBank was run, because it wasn't run really to serve the community, but more as an interesting research project for the people doing it. It's a very different attitude, whether you are trying to provide a service or whether you are mostly interested in the science. So, after a while NIGMS moved the project to a different management group, which was also controversial, and then eventually it was taken over by the [National] Library of Medicine [NLM].

JR: So was the community who used GenBank more satisfied with it once responsibility for it was transferred to NLM?

EJ: That was controversial, too. No, they were not immediately thrilled. There was a lot of tension there as to whether NLM was really doing the job the way the community thought would be best. And there still is, you know. Any time you run a resource like that, you're not going to get 100 percent satisfaction. NLM has done many innovative things, and GenBank has grown enormously in complexity. GenBank is now the name for a huge set of databases and capabilities that are available to people. It's an international consortium that has European and Japanese components. It's very elaborate and absolutely crucial.

JR: So you were there at the very beginning of all that.

EJ: I was there at the very beginning, and it was certainly not envisioned that it would ever become anything like this.

JR: How did you come to be involved in the Human Genome Project [HGP] itself, and why did you think it was a necessary, worthwhile effort? Because when first proposed, it was quite a controversial concept.

EJ: Oh yes, even more controversial than GenBank, probably because it was more expensive. It sort of happened serendipitously. Apparently, people in the community suggested me to Dr. [James] Wyngaarden. At the same time they suggested to him that he needed to create a special organization to handle the Genome Project, and not have it handled by one of the institutes. So I was called and asked whether I would want to take this on, with Jim Watson being the intellectual leader behind it.

JR: Was Dr. Wyngaarden the one who approached you for the job, or did Dr. Watson approach you?

EJ: No, Wyngaarden. I knew Watson, and Watson knew of me. He didn't know me very well, I don't think.

JR: When you were approached with the offer for the position, what did you think? Were you excited? Hesitant?

EJ: Well, both. I was excited, because I thought it was an exciting project, even though it seemed pretty iffy in those early days. I was excited because I was really ready to try something else, but it was risky. Nobody could guarantee me that it would be around a year or two later.

JR: You say that in the beginning it seemed iffy. What exactly do you mean?

EJ: Well, it wasn't clear that there would be money for it. Everybody was very certain that the only way it could get started was if Congress provided a special pot of money. No one wanted to take money away from other programs. At that time, NIH was not in very good shape, budget wise. It wasn't clear whether Congress was going to come through with the money, given the controversy, and the controversy lasted for a number of years. It wasn't as if it was over with after one year. But Congress did come through with the money, and Wyngaarden was very supportive, and gradually the various controversies were addressed. I personally believe the controversy died down when the research results became available and people saw that they were actually going to be beneficial.

JR: So the initial controversies over starting the project began to subside when it began to produce some concrete results?

EJ: When it produced concrete results that people could see the utility of. Until then, they were very afraid it was going to eat up money that they thought could be used better for other kinds of research.

JR: When Dr. Wyngaarden approached you, how did he describe what your position was going to be like? How did he define what your role in the project was going to be?

EJ: None of this was spelled out in the greatest detail. I was just told that Watson would be there occasionally, and that I would be running the operation day to day.

JR: How did your responsibilities change over time as the center and the project grew more organized?

EJ: When we started, it was just me and the secretary and one other scientist, whom I recruited from NIGMS, and they've never forgotten. Initially we didn't have control of the budget; we were just sort of putting out fires. But it soon became clear that this thing was taking root, and that Wyngaarden was working with Watson to have it become an organization that could make its own grants. So we had to vastly expand the staff to handle that, and create all the different kinds of capabilities that a funding organization needs to have. We had to have a budget office, a personnel office, a grants management office, a review office, all those bits and pieces that we didn't have initially. It quickly turned into a major recruiting effort to get all these people on board, and get set up to be able to handle the money, make the grants, develop plans for what should be funded, and get the community behind these plans. One of the first things we did was establish an Advisory Committee, with which we worked very closely to lay out the structure of how the Genome Project would be accomplished.

JR: Was that an internal NIH committee?

EJ: No, entirely outside people. All people with scientific stature who would give us good advice and also be respected by the community.

JR: Why was 1989/1990 the moment when the project was finally launched and the five-year plan published? What was special about that window of time that allowed the project to get off the ground?

EJ: Well, it was preceded by several years of agitation, and a number of meetings took place where this issue was raised. At that particular time, several things came together. The National Research Council had been asked to do a study of the issue and make a recommendation. Or maybe they appointed themselves to do it; I can't remember what stimulated them to do it. They got a group together to debate this issue and come up with some sort of authoritative statement about whether it should be done, how it should be done, and who should do it. I believe the NRC report was published early in '88, but its contents were well known before it was actually printed. At the same time, the Office of Technology Assessment of the U.S. Congress, which no longer exists, also did a study at the behest of Congress on what should be done, and came to a very similar conclusion. Both reports concluded that the project should go ahead, with certain caveats. NIH also gathered some folks together to discuss this issue.

JR: Was that the meeting in Reston?

EJ: The so-called Reston meeting, yes. Wyngaarden wanted to have his own advisers tell him what to do, and a lot of luminaries attended that meeting. I think they sort of cornered Wyngaarden and said, "It's time to act. Got to get behind this, got to get going. NIH is going to be made a fool of if they don't get on this bandwagon." They told him he needed to get behind the project, establish a special office to run it, and get a "working scientist" to run it, which then turned out to be Jim Watson. He was not actually a working scientist, but he was regarded as equivalent to that. He had not been in the lab for a long time, but he ran a research organization and was clearly, intellectually, very much a working scientist. So that's what got the ball rolling.

JR: Who were some of the "luminaries" pushing for NIH involvement in the project?

EJ: I would have to pull out the minutes of that meeting and see the attendees. I do remember that Eric Lander was there. He was a mere babe at that time. Lots of people said, "Eric Lander, he's too young to be wise." But he was very outspoken and clearly came across as a very smart little kid. I remember discussions pro and con, "Is Eric Lander really mature enough to take a leadership role in this?" Well, he grew up quickly. So he was there, and David Baltimore also had a prominent role. He may even have chaired the meeting. Of course, Watson was there.

JR: And this contingent was really agitating for the creation of a new genome center within NIH?

EJ: Yes.

JR: What was their main argument for a new center, as opposed to the status quo with the genetic research in NIGMS and the other institutes?

EJ: Well, they felt this project would be a very different kind of research from the kind that NIGMS supports. If the project was located in NIGMS, which would have been probably the only logical alternative, it would be viewed as draining money from NIGMS programs. And there would be a reluctance by the institute to really push the Genome Project, because it might have a negative effect on their other programs. Rather than put the institute into that conflict situation, they thought it would be best to have a separate organization run this project that would have its own money, so nobody could say the money was being taken from someone else. Of course, some people made that complaint anyway, but it wasn't so localized. It was a more generalized complaint about money being taken away.

JR: Once NIH decided to establish this new genome center, what were some of the competing ideas of how it should be organized? I know there was a conflict between Ruth Kirschstein, director of NIGMS at the time, and Dr. Watson regarding this issue.

EJ: There were two mindsets on that, and it wasn't just Kirschstein and Watson. There were others divided along the same lines. One was that time-honored NIH investigator-initiated research should play a major role, and that scientists would come up with creative ways of addressing this without being told what to do in some kind of centralized fashion. Others believed that it really had to be organized centrally if it was going to get done, because of the magnitude and complexity of the job, and that if everybody did their own thing it would never add up to the whole.

So that was a big debate, and during the first years we were always being asked, "Well, how much of our money is going to investigator-initiated research?" We kept very careful track of that, and made sure that the fraction wasn't too low. We called a lot of things investigator-initiated that might not have been called that by other people [laughs], but we did have a respectable portfolio of smaller grants that were spread all over the country. And the other camp said, "The only way this project is going to get done is if there's a very strict plan, and everybody works according to this plan, and it's all coordinated." And they turned out to be right. It would never have been finished without central coordination. I think in the early years a lot of investigator-initiated research was the right thing, because many new developments were necessary to actually make completion of the project possible. The basic science really hadn't been done yet, so we needed to stimulate that. But later on, the sequencing became a massive organizational challenge.

JR: Given that the decentralized approach was more in line with NIH tradition, how did those advocating for the centralized approach manage to win out in the end and implement their organizational vision?

EJ: It was not like everybody got together and decided, "Okay, we're going to go this route." It was a constant back and forth, a pull in both directions. If things were not going well, some would say, "Well, we should have funded more investigator-initiated research." If the technology wasn't ready, some would say, "We should have done more technology development." Things did not go in a completely smooth trajectory.

We'd have a good plan, everybody would start on it, and then we'd come to some kind of block—some technology wasn't ready, things weren't working quite the way we envisioned—and then there would be all this soul-searching. Then someone would find a way around the block, and we would shoot off again, and something would get done. For example, we'd say, "Oh, we'll never get the genetic map done." Well, then there were breakthroughs, and we got it done according to schedule or earlier. This happened repeatedly. I'm sure there are now people saying, "You'll never get the genome finished on time." It's supposed to be finished next April. They've always come through, and I have great faith they will come through again.

So that's the way it went. All of these arguments went on and on, and the argument about investigator-initiated research is still not dead. I think that there's still room for quite a bit of that in other areas of genome research, or even in sequencing technology, which is not all that people would like it to be, even today.

JR: So this argument over where to devote the money continues?

EJ: The argument over where to put the money goes on all the time. We used to go forth and say, "Half our money goes to investigator-initiated research, and half goes to these organized, big centers." Now, of course, the proportion is very different. I don't even know what it is. Maybe 80 percent goes to big centers. We've come a long way, and we're in a different place now, but the argument about how much should be left to investigators to decide how to spend and how much should be centrally directed goes on all the time.

JR: There was a lot of dissent within the scientific and biological community on the merits of the genome project. How did the project's proponents, such as yourself, address those concerns?

EJ: Every way we could. [Laughs] I don't know whether you ran across a file of letters. There was a campaign by Martin Rechsteiner.

JR: That was in 1990?

EJ: Around 1990, yes. The purpose of the campaign was to get everybody to write in and tell us what a terrible mistake the project was, that it was going to change science as we knew it, and on and on. Well, they were right about that. It did change science, but not quite the way they envisioned. We responded to those letters as best we could, and we had some prepared messages that went out to everybody who wrote us. Even more effective, I think, was that the Advisory Committee and all the major supporters of the program went on the talking circuit and spoke about it wherever they could, to make the case how important this would be.

JR: And that seemed to get the message across?

EJ: That kept things under control. As I said, once results became available, everybody wanted them, and then they quit complaining. So we had a policy early on, and this was part of the very perceptive vision of the people who were proposing the project, that results must become available publicly as quickly as possible. We did not follow the usual process where the person who makes the discovery holds onto it and writes a paper over a long period of time, and then eventually the results become available to everybody.

We decided that results had to go out as soon as possible, regardless of publication, so that they could benefit the scientific community and lead to further discoveries as quickly as possible. This meant that people could get these results much more quickly than was customary.

JR: Was the emphasis on rapid data-sharing a point of easy agreement among project participants?

EJ: Yes. The proponents were all on the same wavelength about that. You could say it was self-interest. They all wanted the results, too. [Laughs] They clearly perceived that rapid data-sharing was going to be the selling point.

JR: In the early days when the Genome Center and the project were getting started, how was the support of Congress and the administration? Were they supportive or skeptical?

EJ: I don't know if I can remember all of the Congressional supporters, but Senator [Peter] Domenici comes to mind. He was very supportive of the project. He was particularly supportive of the Department of Energy role and the role of Los Alamos National Laboratory, which is in his state. Of course, the most important thing for us was the appropriations committees, and that was always rocky. We were in the unusual position, for an NIH component, of the administration actually putting forward larger budgets for us than the Congress appropriated. Typically in NIH, the administration puts forward the budget and Congress adds something to it, which is the reverse of what many other agencies experience. With the Genome Project, the administration was very supportive, at least judging by the budgets they sent to Congress. Then there were always these periods over the summer when Congress would cut violently. Then there would be some restoration. It would go back and forth, and we never knew how much money we were going to get until the very last minute.

JR: What were their reasons for appropriating less money than the administration gave you?

EJ: They would say things such as, "Oh, this request is so big. That's ridiculous. You can't use it." Or they would say, "Well, you know, there are these children or these Parkinson's patients, and so forth, and we have to take some from Genome and give it to them." You know, those kinds of negotiations that go on when Congress passes budgets.

JR: So it wasn't necessarily that they didn't believe in the merits of the program?

EJ: Well, there were those, too. Some of the staffers were very skeptical, and said, "Oh, you don't need to do it this way. It'll get done. You don't have to use this massive approach to it."

JR: So Congress' response to the project was fairly divided?

EJ: I would say it was mixed but they came through in the end. They may have cut from the amount the administration requested, but we always got good increases nevertheless. We've always operated with five-year plans, and we made one of those right at the beginning of the project. That plan had a budget with it. The National Research Council had proposed that the project would cost 200 million a year for fifteen years. We kept watching how close our budget came to that, but it was many years before we got anywhere near 200 million a year.

JR: Overall, would you say the project received the funds that it needed, or were there times of real struggle, when it looked like the budget wasn't going to be as much as you needed to get things done?

EJ: I think we got what we needed. Obviously, we could have used more. It might have speeded things up, but it seemed to match the most urgent needs.

JR: You mentioned the five-year plan. Were you involved in the creation of the first five-year plan?

EJ: Yes. That was done by our Advisory Committee, plus other folks. It was also done jointly with DOE, which added to the complexity, because the way the DOE does things is different from the way NIH does things. So, we had to find a way to do things that would mesh with both agencies. We all went up to Banbury at Cold Spring Harbor and had it out, and tried to come up with some sort of plan. There was much debate and differences of opinion, but we did come up with a plan that worked out as far as guiding the project and forming a set of goals that we met. It took us on our way.

JR: How were the specific goals and benchmarks laid out in the plan decided upon?

EJ: Well, the Advisory Committee had a vision of how the process should work from beginning to end, in very general terms. That vision was very close to what the NRC had initially laid out. It called for some money to be used to work on model organisms, so that we could learn in simpler systems how to generate and use maps and sequence data. It also called for the human project to be done in three steps, with the genetic maps first to put out markers across the genome, so you could tell where you were; and then a physical map, breaking the genome down into more manageable pieces and ordering those; and then finally the sequence. That's the way it actually turned out, more or less, in the end.

People had quite a bit of experience mapping genes, and they could extrapolate from that experience what might be possible for the genetic map over a period of time, given more money. There was a lot of back and forth: "We can do it in two years." "Oh, you can't do it in two. It's going to take you five." And so it went on and on, and people did fancy calculations on the board, and finally we reached some sort of consensus as to when the genetic map could conceivably be completed. Then there was debate about what we meant by complete, and what the map would look like.

All these issues evolved and were discussed continuously, but we had a basic plan. The genetic map was supposed to take five years, the physical map about five to eight, and then we would move into sequencing in a big way. Meanwhile, we would continue to do technology development and study model organisms, so there was an array of things to be pursued.

JR: What were some of the technical advances in the years preceding the Genome Project that made these discussions and these goals even possible?

EJ: Before the project began?

JR: Right.

EJ: Well, certainly the invention of DNA sequencing. DNA sequencing machines really came on the market about the time the project started. During the rest of the century there had been many major discoveries, but I don't know that there was any big event that made people think this was possible. It was more a matter of saying that if we can do it on a small scale, then we can put our minds to it and do the whole genome on a big scale. There was a feeling that if we set ourselves this ambitious goal, it would drive the science forward. There were many detailed little improvements that had to be discovered in order to get these jobs done, but the major thing was to work on a much larger scale than any biologists were used to. When you work at higher scale, it's not just that you do more of the same. You do it differently. You find ways to be more efficient; you find ways of multiplexing, or automating, or doing things in a smaller volume so that it's less expensive. They've figured out ways to do things in large numbers of multiples, and to use robots and as much automation as possible, instead of relying just on humans.

JR: As opposed to the more traditional "one investigator/one gene" approach?

EJ: Yes. [Laughs] Or one graduate student plugging away in an awkward fashion, not thinking about efficiency or cost, but just pursuing his personal interest.

JR: You mentioned that DOE did things a little differently than NIH was used to. How would you characterize the working relationship between DOE and NIH?

EJ: I would say it was very cordial. Everybody was very committed to working together, but the different cultures and systems that the two organizations used to get things done complicated the situation. DOE conducted its genome research through its national labs, and the way the department relates to its national labs is very different from the way NIH relates to its grantees.

JR: How so?

EJ: The national labs are run by private organizations, but they're supposedly part of the Department of Energy, so they're GOCOs—government-owned, contractor-operated sites—and they're more independent of the Department than you would think. The national labs tend to feel like they should be allowed to do what they want, so DOE had limited control over them. Of course, NIH has limited control over its grantees, but it's a different relationship. Also, a lot of things at DOE were done centrally that NIH did in a decentralized way, so the amount of time it took DOE and NIH to do things was different. The layers of approval for different actions varied between the agencies.

JR: I'm going to take this opportunity right here to turn the tape.

EJ: Okay.

[End Tape 1, Side A]

[Begin Tape 1, Side B]

JR: Given the difference in cultures between the two agencies that you described, what were some of the ways that you overcame that to work together?

EJ: One was that we just agreed upfront that NIH would focus on certain things and DOE would focus on certain other things, so that we weren't in each other's hair more than necessary. For example, NIH put a lot more emphasis on the model organisms, while DOE focused on human research. We both had an Ethical, Legal, and Social Issues component, which was Watson's idea but was foisted on DOE as well, but DOE decided to emphasize public education, while NIH focused more on the clinically relevant issues. So that's what I mean by different emphasis. We didn't say, "You can't do this, and we won't do that," but we said, "Our main emphasis is here; your main emphasis is there; we'll have our special areas of influence, and we'll deal with any overlap."

JR: So that arrangement worked fairly well, as far as working together?

EJ: That worked pretty well, yes.

JR: You mentioned James Watson. What was his role in the early development of the Genome Center and the project, in terms of his being such a recognizable name?

EJ: I think his influence and support had a lot to do with the decision to launch the project. He was the leading advocate for it, and he could get people of stature to come and help with the project, because they wanted to work with him. And because he was so respected, people listened to him. It was not like he dictated things, but he would insert some comments here and there that made things happen. [Laughs]

JR: So his stature in the field really went a long way?

EJ: Absolutely. It would have been very different without him.

JR: So why did he then resign as director of the Genome Center in 1992?

EJ: Well, that was an issue between him and Bernadine Healy. She took great offense at some of the things he did, particularly the issue of patenting ESTs, and then decided that he might have been acting out of a conflict of interest and started questioning his impartiality, which was really ridiculous. She somehow took it into her head that there was something going on there, and he resigned.

JR: The conflict of interest, was that over some stocks that he owned? Something along those lines?

EJ: She felt that he might be advocating the positions he took because of some stocks or other investments that he had, which was rather silly, but that's what she believed. There were several investigations into his holdings.

JR: So that was one of the main factors behind his resignation?

EJ: I think that was a factor, yes, but the fact that they really didn't see eye to eye on a lot of things was the underlying cause.

JR: Once Dr. Watson had left and Francis Collins arrived, how would you compare and contrast their leadership styles in running the center, seeing as how you worked under both of them?

EJ: Well, they're very different people, but they were also doing a very different job. Watson was basically a consultant to NIH, and remained at Cold Spring Harbor, coming to NIH occasionally. Collins was hired as a federal employee, so he was here full-time. Collins also had the charge to create an intramural research program, on top of the grants program that already existed, so he was much more hands-on and much more involved in NIH as a whole than Watson was.

JR: This is probably as good a time as ever to discuss the controversy over patents and intellectual property rights that arose early in the genome project.

EJ: Healy had in mind that NIH should push patents and should use that as a way to generate income for NIH. She just had this approach to how things should be done, and she had hired staff who were running the NIH patent office who shared that viewpoint, or maybe even promoted that viewpoint to her, I don't know.

The [J.] Craig Venter patents were the primary factor that stirred the controversy. NIH decided, in its wisdom, to file for patents on these little snippets of genes. Whether they were urged to by Craig or not, I don't know—he professes that he was against it. Watson thought it was an absolutely ridiculous idea. Watson's very outspoken. When he thinks something's ridiculous, you know it.

JR: Was Bernadine Healy's position on patents the unified position of NIH, or did NIH even have a unified agency position on patents at that time?

EJ: That was the director's position. I don't know that there were many people at the NIH who would have thought that was a good idea.

JR: What did the National Genome Center think when this controversy came out?

EJ: We didn't like it, but we were never asked, which was one of the problems. Healy decided to file on these things without really consulting anybody who might have known the implications of it. One of the things that annoyed Watson is that she never talked to him about it, even though he felt it was a very significant development for genetics.

JR: What did the center think about Craig Venter's method that he was using for the patents, the cDNA [complimentary DNA] sequence?

EJ: cDNA. They also called those snippets of sequence "ESTs" [expressed sequence tags].

JR: What did the center think about that method of obtaining sequence, and the claim that something like that was novel enough to warrant a patent?

EJ: None of the people we worked with felt that it was justified to get patents for those snippets. But aside from whether they were patentable, there was a question of the value of Craig's approach in obtaining the human sequence. That was more complicated. I think people saw that these pieces of sequence had some value—how much value was debatable—but they were also concerned that Craig was going around saying that he was going to sequence the genome by doing these little snippets, and that there wasn't any need to do anything beyond that. That's what got people really stirred up, because most did not believe that was true.

The ESTs were just a small fraction of the genome, and we wanted the whole thing. We were afraid that such talk could persuade the movers and shakers that Craig was right, and that therefore there wasn't any need to invest in doing the whole genome sequence.

JR: You mentioned that Collins began the intramural program. That was 1993, correct? What was it about that moment that warranted the creation of such a program? How did the intramural program differ from the extramural program?

EJ: It was actually an idea that Watson proposed to Healy. So the idea was there, and it was part of the negotiations between Collins and Healy that Collins would start this program. There were a number of reasons why it was a good idea. NIH was not particularly known for being at the forefront of this field, and yet NIH has a very large research community here in Bethesda. So it was felt that this would infuse some new blood, new skills, and new capabilities that would benefit the whole community if they got some genomic scientists to come to NIH. I think Watson also felt that if the Genome Institute, which at that time was still a Center, had its own intramural program, it would have a better chance to survive. I think Collins shared that view, that it made a more rounded package with more staying power.

JR: Were the issues and research topics that the intramural scientists worked on substantively different from the extramural programs?

EJ: Yes, they were. They really were not doing Genome Project work, in the sense of the five-year plans. They were doing related work that used the Genome Project to solve more biological questions, such as looking for disease genes, studying their effects, and so on. It was quite distinct, and that was done deliberately, because the idea of having one of these large production-type operations on the NIH campus raised all kinds of problems. That sort of thing is really better done outside the federal system as a contract or a grant, where you have the flexibility to change your staff more readily than you do with federal employees. Those were some of the reasons why it was decided that the intramural program should be working on somewhat different questions. I think as time goes on, those distinctions are going to become more blurred because of where genome research is going, but initially it was important to keep it separate.

JR: You mentioned the center being upgraded to institute status. Did that really represent a real change in the organization's operations or was it just more of a formality?

EJ: It was more a matter of image and stature, because most of what an institute would have was already there. There were a couple of little things that the institute acquired when it changed its name, but that was not really the major reason for doing it.

JR: So the daily operations of the center didn't change much?

EJ: Didn't change, no. It was more that it was now equivalent to other institutes, and not like a second-class citizen.

JR: I want to backpedal a bit to talk about the ELSI program, as it seemed to have been a priority from the beginning of the project.

EJ: Yes.

JR: Why was that? Why was this seen as a priority that needed funding and special attention?

EJ: That was another area of controversy when the Genome Project started. There were all these ethical concerns about what it would do to us to know our genome, what we would do with the information. Now it seems kind of odd, looking back, but in those days what people were afraid of was that we would use the information to create bizarre new species, to clone animals and humans, and do all kinds of wild things that would change nature significantly. People were less onto the fact that it might create ethical problems in medical practice.

When Watson went around giving talks, he would get these questions. "How are you going to avoid misuse of this information?" On an inspiration, he said, "We're going to study that. We are going to put some of the money into research on these issues." That's where the ELSI program began. Initially, he said, "We will divert 3 percent of our money," but in a very short time he upped that to 5, because 3 didn't seem to be quite enough. That was one of the wisest things he did. I think it really saved us from what could have been some catastrophic situations, because we gave the critics money to study these matters. Also, the wise people in that field started saying and writing sensible things. There were a lot of conferences and books written, which swamped the area with some solid information instead of speculation.

As money became available, new people were attracted to the field, so that it now has a solid foundation of scholarly thinking that's available for people who want to study in this area. This was absolutely not available before. All you had was ranting and raving, wild ideas without any basis in fact. My view, and it's shared by many, is that having the ELSI program has really saved the Genome Project from being destroyed by those issues.

JR: When did ELSI's emphasis shift towards issues such as medical privacy and potential insurance abuse? When did these more practical issues really come to the forefront?

EJ: It was just all the activity, getting people involved who were a little saner and spoke up about the practical issues. We created an ELSI working group of people from various fields who had an interest in these matters, and they went around holding meetings and funding other people to hold meetings, so there were many scholarly discussions. Whenever there was an ELSI discussion, the press would just descend and write stories about it. So gradually the nature of the conversation just changed, as people became more fact-based and reality-based, and learned what the real issues were.

JR: Was ELSI strictly a program meant to study the issues and put forth positions, or was it actually involved in policy making?

EJ: Yes, interesting question. The ELSI working group would have loved to be a policy-making kind of body, but it was not authorized to do that. [Laughs] For one thing, policy is made by the president and Congress, and not by little groups talking among themselves on the NIH campus. So there was a little bit of a tension with them on that subject. We kept saying that our purpose was to support research and generate scholarly work that could be used to inform policy makers. A lot of that did happen, but the Working Group sometimes said, "We should be able to make pronouncements that have an effect, and people should listen."

JR: Did their work have an effect on the people who wound up making policy?

EJ: Yes, over time I think it did have influence. Now you might say, "Well, it hasn't had much effect because we still don't have any law protecting us from discrimination based on genetics. We still don't have health insurance that people can depend on regardless of their genes," and those kinds of things. But those are extremely complicated issues, given our society's history, and even though Congress keeps making a good run and almost getting there, they never quite make it. That's just going to take time. There are people out there who say, "Well, this is all a waste of time, because the laws haven't been passed and nothing has happened," not appreciating that these things do take time, and changing people's views is an arduous process.

JR: Shifting gears a little bit, what was the importance of the mouse genome project, going side by side with the human genome project, as opposed to some of the other simpler organisms?

EJ: Well, the other simpler organisms had been done by that time, and we had never really come to grips with whether we would sequence the mouse, or when we would sequence the mouse—before the human, after the human, at the same time as the human. There was a lot of scientific pressure for doing the mouse in parallel with the human, because people felt that only by having both of them could you really interpret what each meant.

The mouse community was bolstered by the human genome community, who also felt they needed to have the mouse sequence as a comparison to the human to make any sense out of it, and the mouse people became more vocal. The coming of Harold Varmus as NIH Director also played into that, because he's a mouse geneticist, and so he was very interested in mouse information. He also formed a trans-NIH committee to coordinate mouse resources. So Harold Varmus' interests and community pressure came together and created an opportunity to make some money available to move the mouse sequence along a little faster. The interest of private companies in chipping in some money also helped to move us along faster, as they felt it would be extremely valuable to have. So there was a big push to do some fast mouse sequencing and get a rough draft out.

JR: How does having the mouse sequence help the scientific community to understand the human sequence better?

EJ: They're quite similar. They're about the same size, and most of the genes are the same. Also, when you have this mass of information on the human genome, you don't know just by looking at it what's important and what's less important. Computer programs can help, but they're not 100 percent accurate by a long shot. By comparing human and mouse sequence in a region that you know has the same function, you can see areas that are the same or almost the same, and areas that are very different. Then you could say, "Well, if it's the same in human and mouse, it must be a very critical function that both need." Other areas that are very different in mouse and human may not be as critical. People find these comparisons extremely valuable in order to get a hint of where to look for things.

JR: Thus far we've been talking about the project in terms of what was going on here in the United States, but really it was a massive international effort. What was the relationship like between the Genome Institute and the various international partners? How did you coordinate the effort here with the efforts going on around the world?

EJ: That's an interesting story. Initially there was an organization called HUGO [Human Genome Organization] that Watson was trying to establish, and that the scientific community envisioned as coordinating all of this. I think it was really doomed from the start. The whole concept was flawed because no government agencies or funding organizations in other countries were going to let themselves be told what to do by this voluntary group of scientists who saw themselves running the project internationally. That just wasn't realistic.

We are all answerable to our Congress, our president, and officials like that, not to HUGO. The other difficulty HUGO had was it really never was able to raise enough money to make it an effective organization. Its leaders had envisioned that NIH, DOE, and places like that would just give them money to operate, but there was no way we could give money to run a private organization. We can only give money for projects, so that didn't work out.

HUGO still exists and works away at some issues, but it never became the sort of glue that held everything together. Instead, the agencies communicated with each other, and we tried to keep up on what was happening in Europe, in Britain, etcetera, with some success. We weren't always able to keep up with everything. Sometimes things would suddenly pop out that nobody had been fully aware of, but there was a great willingness and interest in not duplicating.

When some of the bigger projects came along, the international partners were very willing to coordinate what they were doing, especially when it came to sequencing. Only a few countries could afford to do anything significant with sequencing because it was so expensive and so massive. Initially, most of the countries that claimed they were working on the Genome Project really were working on human genetics—genetic diseases, finding genes, those kinds of things—which we really didn't consider part of the core of the Human Genome Project. So there was no need to coordinate those efforts; they were just doing their usual thing.

JR: So it was really only a select number of other countries that were doing activities along the lines of the five-year plan?

EJ: Right. It was mainly Britain. France made very significant contributions in certain areas. Japan was always trying to be onboard, but their whole budget and organizational structure is just so bizarre. Until recently when human sequencing really picked up, they never quite got their act together. Now they have a very respectable sequencing center that's making major contributions. There are some little centers in Germany that have also contributed, but they've never been major players. The Germans have three little groups rather than having one big group. If they put those groups together, they could do bigger jobs. But that's not where they are at, which is fine. There's a need for all kinds of research. So international coordination of sequencing the human genome became a real challenge, and the NIH staff and Francis Collins played a major role in holding it together. Before sequencing it was not as much of an issue, because there were fewer players.

End of Interview #1

National Human Genome Research Institute (NHGRI)

Interview #2 with Elke Jordan

Conducted on October 30, 2002, by Jennifer Rogers

JR: Last time when we talked about the first five-year plan, I noticed that there was a strong focus on genetic mapping and physical mapping in the early years of the Genome Project. Why was it so important to do the mapping before sequencing, and was any sequencing work being done while the mapping efforts were going on?

EJ: Sequencing efforts were going on at a small scale. For example, there was a project to sequence the bacterium *Escherichia coli*, but we didn't yet know how to sequence very well, and the technology was simply not ready for human sequencing on a large scale. The maps were important to give us signposts along the genome, so that we could tell where we were. It was like building a network of roads so that when we did begin sequencing, we could tell where the sequences belonged.

When you sequence something as large as the human genome, or even genomes that are much smaller, you don't start at one end and go systematically through to the other. What you have to do is break the DNA into many small pieces, small enough for the machines to handle, and then put the pieces back together. Without a map that tells you where the piece came from, you would not have a very good chance of putting it back together correctly.

JR: It's very difficult to reassemble the sequence without the maps to guide the way?

EJ: Right. There have been attempts. One of the things that Celera [Genomics] claimed they were going to do was break the DNA up into pieces, sequence the pieces, and put it back together using just computer logic without any maps, but that has not yet turned out to be possible for large genomes. You need some map information. Whole genome approaches do work well for smaller genomes.

JR: The method Celera used is known as whole-shotgun sequence, correct?

EJ: Whole-genome shotgun, yes.

JR: So that has not proven successful for Celera in putting the sequence back together?

EJ: They did put the sequence together, but they used map information from elsewhere to help them. In fact, now the human, mouse, and rat sequencers are using a combination of whole-genome shotgun together with selected map information to assemble sequences. The map information they're using is somewhat different from what we originally envisioned, but it's the same idea. You have something to hang onto. [Laughs] "I know I'm on Fleming Avenue. I don't know where, but I'm on Fleming." Whereas if you didn't know it was Fleming, it could be anywhere in the Washington area. It's just like jigsaw puzzles. If you have an infinite number of pieces that all look very similar, and you don't have any idea whether they're from the upper right or lower left, it's much more difficult to assemble the pieces.

JR: So while Celera chose to do the whole genome shotgun strategy using maps generated by other people, the public project chose to do the clone-by-clone shotgun?

EJ: Originally that's how we started, but we later added some whole-genome shotgun approaches.

JR: Why was a revised version of the first five-year plan issued in 1993? Was it because so many of the original goals, particularly the mapping goals, were ahead of schedule? How was it that you were able to make progress in some areas much more quickly than originally envisioned?

EJ: Our ability to estimate these time frames is limited, because there are many unknowns. This was not a straightforward engineering project, but rather a project that relied on new discoveries as we went along that improved the methods and allowed us to do things not possible previously. It's very hard to predict when those things will occur.

JR: Were there any big advances or breakthroughs in mapping technology itself that helped?

EJ: Originally people thought there would be revolutionary insights that would completely change the picture, but it turned out to be all incremental improvements. The difficulty in predicting these things aside, I think the fact that we launched the Genome Project and started investing money in the research really galvanized scientists to apply their best thinking to the problem. As a result, things began to move much faster than was the case before and our progress speeded up tremendously.

JR: Why was the decision made to add new goals to the revised plan, rather than just saying, "Okay, we had a five-year plan, but now we are progressing so rapidly we should change it into a three-year plan and finish sooner."

EJ: It was always a five-year plan. We decided to take another look at the whole picture. Every time the plan was revised it was an elaborate process that took many months—now it takes about a year—and it involved many meetings with experts in the various components of the plan in order to get their best thinking on what might be possible. How fast are things really going and how much are they really costing? What could we do better? Are we doing it the best way we know how, or are there improvements we can implement?

These discussions were then synthesized into some sort of time line that addressed important questions: where would we like to be and how soon do we think we can get there, given what we know today? What improvements can we project into the future? For example, the discussions about when sequencing could begin in earnest, and how fast it would go, tended to be very heated. There were the optimistic visionaries who always thought we could do dramatically more than we were doing at the time. They just had confidence that things would improve that much. Then there were the cautious pessimists, or cautious optimists, maybe, that always said, "Let's be sure that we can really do this. We need to have a vision of how we're going to get from here to this goal, and not over-promise, because that might hurt the project as well. If we keep saying we're going to do a thousand things, and then we can only do a hundred, that will not be beneficial to the project, and will be discouraging to the community."

It was always a trade-off between those two positions. As it turned out, the optimists were more right than the pessimists. Things did always move much faster than we dared to hope, especially when it came to sequencing. Keep in mind that originally the project was estimated to take fifteen years, which would have been 2005, and they're now on track to declare it finished in 2003. Not only will the human sequence be finished two years early, which out of fifteen years is a respectable percentage, but a lot of other things have been accomplished that were never even envisioned, such as the mouse, rat, and a number of other sequences. The haplotype map is now underway, which wasn't even spoken about in the early days because it was considered way beyond finishing the sequence. So not only was the sequence finished early, but all these offshoot projects started that were not part of the plan originally.

JR: So as the technology progressed, different projects became viable that may not necessarily have seemed possible in the beginning?

EJ: In part, some of these things were possible because we did get financial contributions from industry. For example, some partnerships were formed to produce a SNP [single nucleotide polymorphism] map and expedite the mouse sequence. So the involvement of private industry was very helpful.

JR: Before large-scale sequencing started, there were a series of pilot projects to test the feasibility of it. I believe those started in 1996?

EJ: Yes.

JR: What was it about that moment that made the optimists and pessimists finally come to a compromise and say, "It's time to start the pilot projects and see if we can do the large-scale sequencing"?

EJ: The pilot projects were a compromise between just forging ahead and continuing the way we were. It was decided to let several sequencing groups get started, doing it the way they thought best, and see which ones really came through. And that's exactly what happened. Several of the groups emerged as front-runners, and some of the others eventually dropped out because they were not able to mount the kind of large-scale effort that was needed to be really efficient. We were very cost-conscious. We didn't want to spend more money than was necessary, and we wanted groups that could do it rapidly, but also cheaply.

JR: Which groups stood out as the most efficient, rapid, cost-effective, etcetera?

EJ: Among the NIH-funded centers, the three that are now doing most of the NIH-funded sequencing clearly came out to be the winners. That would be the Whitehead Institute, led by Eric Lander; Washington University, St. Louis, led by Bob Waterston; and Richard Gibbs at Baylor. Those groups just proved themselves over time to be efficient, cost-effective, and able to operate on a large scale, which may be different ways of saying the same thing. As it turned out, the larger the scale, the more cheaply you could do it. The DOE Joint Genome Institute and the Sanger Centre in England also became leaders. Later on, centers in Japan and China became very productive, as well as a center in France.

JR: Scale is important because you're able to automate more tasks?

EJ: Yes. It becomes cost-effective to invest in large-scale automation, and you can make better bargains about prices with vendors. That's just the nature of moving from small-scale to large-scale, because there are efficiencies that arise by doing something in many multiples, as opposed to just one or two. People become more efficient, machines become more efficient, and so on.

JR: How long did these pilot projects go on before all sides were convinced that it was time to start large-scale sequencing?

EJ: I can't remember exactly. I think it was about two years later that we expanded some of the pilot projects dramatically.

JR: As the sequencing technology became more developed and started producing all this data, I'm assuming the need for better databases and means to hold and capture the information became very important as well. What advances had to occur in database technology to handle all of the sequence and the map information being churned out?

EJ: Much of the development of sequence databases happened at the NCBI, the National Center for Biotechnology Information, and the corresponding place in England, the EBI, European Bioinformatics Institute, which had for many years been housing sequence data. In addition to dramatic expansion of these central databases, the various sequencing centers also had to develop elaborate software for tracking the process of sequencing, tracking their samples, tracking the sequence, tracking the maps. Consequently, they really spent a very significant fraction of the money we gave them for bioinformatics, which again had the ripple effect of dramatically improving the funding of that field and attracting a lot of new people into it. That whole field really had to keep pace and did keep pace with what was needed to get the sequence done.

JR: Was there a lag time when some of the sequence information wasn't catalogued as well as it should have been while the databases caught up?

EJ: I think if you were to talk to the sequencing groups, they were constantly struggling to keep up with things, but you cannot really develop these information systems before you have the data. You hear that over and over again. "Give us some data and then we'll develop the system to organize and analyze it, but without knowing what the data looks like, you can't build the information system." They had to go step-in-step.

JR: About the same time that large-scale sequencing started for the public Genome Project, Venter announced that Celera was going to sequence and publish its own version of the human genome. What would you say were some of the substantive differences between the public and Celera's effort to sequence the genome?

EJ: One significant difference was that Celera was just one place, so they were in control of the whole show. From the management point of view, that was a lot easier than trying to control twenty groups spread around the world, who all had individual ideas about how they would like to do things. Fortunately, these twenty groups around the world were really five major groups, so the coordination was a little easier.

Another difference was that Celera professed that they were going to do this whole-genome assembly at a time when the public project was not. Although that approach had certainly been discussed, the public project really had not embraced it wholesale. For one thing, our technology was all invested in doing the clone-by-clone method. There was also another underlying controversy regarding whether or not to do a draft sequence. Those who insisted that we sequence at high quality and finish each clone before going on to the next one were afraid that if we did a draft sequence with gaps and errors in it, there was a danger that no one would ever bother to go back and finish it, because they would lose interest.

The other camp said, "But the information is so useful. Everybody needs it. It will have such a major impact on the field that we really should get it out in an incomplete form, and then finish it up later." So that was a debate going on in the public sequencing groups, and different groups had different views. Then Celera came along and said, "We're solving this by doing whole-genome shotgun. We won't finish it, and we think we can do that much more cheaply, efficiently, and quickly."

That caused the public group to go back to their arguments, and say, "Maybe we should take another look at this proposal to put out sequence in draft form and then go back and finish it, because given the capacity we now have for sequencing, we could get a draft sequence out much faster than the timetable we're on now." So that argument won out the second time around, and everybody agreed that was what we would do. There were still those who said, "We may never go back and finish it," but I think history will show next April that they did go back and finish it.

Now, the public project already had invested in making these maps and getting all that groundwork laid, so those were still used very much to produce the draft sequence. The public draft sequence had whole-genome shotgun components, but it was not done completely by whole-genome shotgun. For one thing, about a third or so was already well underway before we adopted this strategy, so there was no point going back and doing it over again by a completely different method.

Of course, Celera had access to all the public maps as well, so they were really starting from a different point than the Genome Project did in 1990 when it began. A lot of the publicity said, "The public project has been dawdling around for eight years, and now Celera's coming in and is going to do the whole job in two years." Well, that's not true. Celera started at the point the public project had reached at that point, and went forward.

JR: They were building on all the work the public project had already done.

EJ: Right. And all of the technology development, all the maps, all the know-how was publicly available to anybody, so there was a bit of an exaggeration in terms of a so-called "race."

JR: You read my mind. I was just about to raise that issue, because as soon as Celera made its announcement, "race" was a word that got tossed around quite a bit. Was that just media hype? Was there really a race on between the public and private projects to get the draft sequence finished?

EJ: I think that Craig Venter implied that he was going to outrace the public project, and that's probably what got it started. It's a nice image that makes good headlines.

JR: Do you think having a private competitor made the public project go faster, or do you think the public would have gone as quickly as it did anyway?

EJ: Who's to know? I think that it certainly spurred people to do the very best they could. To a large extent, the pace of the public project was governed by the dollars available. Because of the controversy around Celera, both the Wellcome Trust and the NIH made more funding available for the sequencing.

JR: Craig Venter's a controversial figure who emerges at various points in this story. We talked about him last week regarding the patenting controversy . . .

EJ: ESTs, yes.

JR: How would you characterize Venter's overall role in the Genome Project? There are some who think he's made quite a great contribution and there are others who are not quite so generous. [Laughs] What's your view?

EJ: He's stirred up a lot of controversy. On the other hand, he called attention to issues that might not have been raised and might not have been resolved at that time if he hadn't done it. So I think he had an impact, but perhaps we're still too much in the middle of the issue to really evaluate what it was. He certainly has a very original style of going about things, and that's very irritating to people. My personal opinion is that if he had been more politically savvy about the way he approached things, his impact might have been even greater, but that just wasn't the way he liked to operate.

JR: What issues in particular do you think he called attention to?

EJ: The issue of patenting raw sequence. The public project had assumed that raw sequence without any functional information was not patentable. But Craig and Bernadine Healy—I don't know which of them came up with the idea—challenged that, and the issue is still not completely clear. The Patent Office has yet to give a definitive response; however, no patents have been given, to my knowledge, on sequence with little or no claim of functional information or utility. There are several ongoing court challenges, so we really have to wait. It's a very lengthy process because there are several layers of appeals to go through before we get a final answer from the Supreme Court.

JR: Did NHGRI have a position on when a gene became patentable?

EJ: We didn't have a formal opinion, but the general consensus in the field was that it would not be patentable until you had substantial functional information, with experiments to back it up.

JR: What was NHGRI's response to the ethical dilemma of whether genes should be patented at all?

EJ: That's another murky discussion to get into. [Laughter] There certainly are people who feel that it's simply unethical to patent genes, because they're a part of ourselves. That's one of the threads of argument about why DNA without functional information shouldn't be patentable. But it's not the only one.

JR: I'm assuming that it would be very difficult to get private-sector involvement in things like gene therapy if gene patents weren't available?

EJ: Some kind of protection needs to be available to convince people to invest in development of therapies. I'm not a patent lawyer, but patent lawyers tell you that if you have a patent based on the structure, it's a much more solid patent than if it's just based on functional information, because that's more fluid. That's why people like to go for patents based on structure.

JR: Given some of the animosity towards Celera, what made the joint announcement of the competition of the rough draft human sequence possible, with representatives from DOE, NIH, and Celera all present? What happened between 1998, when the two sides did not appear to like each other very much, and June 2000, when there was this cordial joint press conference?

EJ: There was a lot that happened behind the scenes, not all of which I even know. If you really want that story, you have to talk to the principals involved. A lot of people were involved in negotiating a truce between the two sides, because many felt it was better for science as a whole to have some kind of joint announcement about having the rough draft sequence done rather than continue these competing claims about who was first and who did what when. I think both sides decided that the joint announcement was in their interest, and there were, I'm sure, all kinds of pressures applied politically and otherwise to try and get this resolved.

JR: So there was a general consensus that all of the media hype and "race" language may have been detracting from the project's accomplishments?

EJ: Right.

JR: What were some of the differences between the public and private drafts?

EJ: On the whole, there was a lot of agreement, but there were differences, and both sides claimed theirs was better. Looking back from the historical point of view, it's unclear whether any of these differences are going to be that significant. I think the most significant historical perspective is that the public sequence will be finished as close to perfect as humanly possible with the technology currently available and it will be freely accessible to the public. That will be the sequence that scientists will refer to, not the drafts, which were a phase that we went through. The ultimate final sequence will benefit from all of the information that everybody has produced over time.

Even the Celera sequence, to the extent that it's been available, has helped people to learn what has worked and what has not. Different methods work more or less well in solving different technical problems, so some regions of the genome may have come out better using the Celera approach, and some regions may have come out better using the public approach. That's one reason why putting the two methods together will give you an even better result.

JR: So the final gold standard sequence is going to have contributions from all of the different parties, whether they were public or private?

EJ: I don't know that it will literally have Celera's sequence in it, because I don't know that it's available to be put in there. Even without using the actual sequence, there are things that have been learned from just watching that experience.

JR: There was some controversy surrounding where the drafts would be published. How did they each wind up choosing a journal for publication? The private was in *Science*, the public was in *Nature*.

EJ: Well, there was another controversy about publication. [Laughter] The custom in science is that when you publish, the information that came out of your research is publicly available, which means that even data not included in the paper is available to those who want it. For DNA sequence, the convention has become that the sequence has to be in GenBank, because it can't be printed in the journal. It takes too many pages, and it's useless. So that was generally agreed to, and almost all journals, if not all journals, have insisted that authors put the sequence in the public database. Well, Celera's sequence did not go in the public database, and access to it was controlled. Depending on what kind of access you wanted, you had to sign agreements or pay certain fees. There was a point of view that a publication based on sequence that wasn't in a public database was not appropriate, given the standards of the community for putting all sequence in public databases.

Some journals stood by that position, regardless, but *Science*, which published the private sequence, felt that an exception was warranted. That made certain other people mad, because they felt that was just the beginning of more exceptions that would be detrimental to progress. That issue has still not been resolved, and there are still these strong feelings and editorial views where *Science* is willing to make more of a concession than some other journals.[1]

JR: Was the public project planning to publish their draft in *Nature* anyway, or was it the *Science* decision to publish the Celera draft that prompted it to go to *Nature*?

EJ: I think that certainly played a role. Both journals are highly respected. Some people think one is better and some people think the other is better, but the fact of the matter is that *Science* has the larger circulation. If you want to reach the largest possible audience, then you tend to lean towards *Science*, except for this little contretemps that's been going on for a while now.

JR: So the public project is on schedule to finish by April 2003?

EJ: That's what I hear, yes. They've got projections all over the place, and they all lead to April.

JR: How did having the draft sequence change the nature of the work that people were doing on the sequence? Once you have the draft, how do you then go about perfecting it?

EJ: There are really two major steps that were needed to finish. They needed to go back and generate more sequence from the clones that they already had sequenced in order to make a deeper level of sequence on top of the draft, and then reassemble that with computers. Many of the errors and ambiguities fell out after doing that step. But there were still regions that weren't right and gaps that weren't filled, and at that stage it's more or less a hand job. You take each clone, look at it, and decide why it's not complete. You also look at the gaps and try various tricks to fill them in, and that's what's going on now. So it's less predictable, it's less automated, and it requires greater skill to do these last steps. It was always envisioned that somewhere between 90 and 99 percent of the sequence would take less than half of the work, and then finishing would be at least an equal amount of work.

That's proved to be true, although a greater proportion of the work has been automated. It's been possible to automate up to a higher level of accuracy than was envisioned, even several years ago. They've pushed and pushed to make more and more of it automated, which is not only faster, but also allows you to predict more accurately how long it will take you and how much it will cost.

JR: Now that we've taken our story all the way up to the projected completion of the human sequence, I want to take a step back and ask you some questions on the broader significance of the project and how it changed science as a whole. For instance, in genetic and physical mapping, what do you consider some of the most important advances that the project brought about in these fields, as opposed to before the project?

EJ: Genetic mapping has changed quite dramatically. When we started, everybody was using RFLPs, restriction fragment length polymorphisms, to map, which were laborious. Each one had unique properties and experimental conditions, so they did not lend themselves to automation or large-scale production. Now we're onto SNPs, single nucleotide polymorphisms, after going through several other kinds of markers, which can be automated. Assaying them can be automated and carried out on a large scale very rapidly, so genetic mapping has moved into a whole different sphere. We still complain that we can't test enough SNPs rapidly enough to do the kind of experiments that people envision now, which were not even on the horizon when we started.

EJ: Physical mapping also looks entirely different. We were working with YACs, yeast artificial chromosomes, which one rarely hears about now. Then we moved on to BACs, bacterial artificial chromosomes, which seem to be more stable and easier to handle, and they're still in widespread use. In addition, completely new methods have come along, such as radiation hybrid mapping and fingerprinting, all technical terms which I won't attempt to explain. But again, these methods can be applied much more rapidly, in a much more automated fashion, and can give you maps much more quickly than we used to think possible.

JR: What were some of the problems that you had with the yeast artificial chromosomes that made it necessary to seek out these new, better methods?

EJ: They were difficult to work with. They tended to break down. They had rearrangements in them, so they were not always true representations of the genome. They were a tremendous boon at the time, because there wasn't any large cloning vehicle to hold significant amounts of DNA, and the larger the pieces, the easier it is to put them back together. So it was important that they were there, and they still have utility in special circumstances, but they're not the workhorse cloning vehicle anymore.

And in sequencing we now have these very powerful machines, based on capillary electrophoresis. Coming down the pike are new technologies, for example miniaturized sequencing on a chip. Instead of having to do your reactions in several steps, they would all be done together on one chip.

Mass spectrometry, single molecule sequencing, and all kinds of other things are also being worked on. I expect in the not-too-distant future, a couple of years, sequencing will look completely different again. The speed at which sequencing can now be done is just phenomenal compared to what anybody even dreamed of when we started.

JR: What were some of the major contributions of the Ethical, Legal, Social Implications [ELSI] program as it evolved throughout the project?

EJ: That's a little harder to be concrete about. Maybe the most important contribution that program has made is to create an expectation that you have to consider ELSI issues when you launch into a new area of research. You can't just ignore them and hope someone else will take care of them later on.

So it's become the norm now, when dealing with research areas that affect humans, that you look at ELSI issues side by side with the research, and I think that's a tremendous change in perspective. That was simply not the case when we started. As far as actually solving major problems, as I said last time, these problems are not the kind that you solve overnight. It takes many years of debate and small incremental changes in the law until you finally get—hopefully—what everybody would like.

JR: Looking back on the project, did it have any shortcomings, any areas where it didn't quite fulfill its promise?

EJ: You can always imagine that people could have been more clairvoyant and have foreseen some of the things that happened, but I don't know how they would have. No, I really don't feel that there is anything that you can clearly point to and say we should have done it differently given what we knew at the time. Hindsight is always wise. There are clearly things we could have done differently, and who knows what might have come out? But overall it went remarkably well, and in spite of all the controversy, more smoothly than most people hoped when we started out. There were times when one certainly felt, "This may be the end of the project. We may not survive this particular controversy." But we did.

JR: While there were many controversies throughout the project, do any stand out as being particularly dark moments in terms of the project's survival?

EJ: There were a number of difficult moments along the way. Sometimes looking forward, an issue looks like a mortal threat, but looking back you can see that it really wasn't. I'm sure the whole Celera episode at times looked like it could be a deathblow to funding of the project, but from this vantage point, I don't really think that was within the realm of possibility. Not that it didn't cross people's minds, not that people didn't talk about it, but I think we were too far committed at that point to go back.

Similarly, there were a lot of people who were unhappy in the early years, and a lot of people who were writing letters, and a lot of people who were complaining, but the project had a momentum that carried it through. There could have been other political circumstances. There could have been world events that could have changed the course, but fortunately none of those things happened. I think we've learned a lot, and if we were to launch a project like this now, we would do it differently, but at that time we didn't have that experience.

JR: While they were all doing important research, which of the various NHGRI-funded centers do you feel made some of the most important contributions overall to the project? Do any of them really stand out as being just exemplary in their contribution?

EJ: Yes. There are so many, and the contributions are so different, you know. Certainly Eric Lander stands out. He's been there since the beginning. He's still there, which is remarkable in itself. He participated in each phase of the project and contributed a lot of ideas, some of which panned out, some of which were not as well accepted. But he had a very stimulating effect on things.

Another person whose thoughts and wisdom were always sought and had a lot of influence was Maynard Olson. He didn't end up leading a big center, but his intellectual contributions were very significant.

JR: He was involved in some of the very early sequencing work, correct? In the eighties?

EJ: Yes, he was, and he developed the YACs. Then there was the development of the sequencing machine with [Leroy] Hood and [Michael] Hunkapiller. They weren't really part of our inner group of grantees. Hood did have a grant a lot of the time from us, but he wasn't part of any of the major sequencing groups. He was doing a variety of things. But without that machine, this project wouldn't have been possible.

So, those are very different contributions. Eric Lander produced enormous amounts of data and ideas. Maynard Olson developed significant technology and just generally had a vision of the project that was very influential. And Hood and Hunkapiller and many other people contributed critical technologies, so they're very different contributions that have a different degree of public exposure, but they were all critical to making the project work.

I should add that there were major contributions from other countries as well. It was by no means all invented in the U.S. We tend to be very insular in our view sometimes, but there were very significant contributions by the British and the French, especially, without which things would not have gone as well.

JR: Some of the British centers took on quite a bit of responsibility for sequencing.

EJ: Yes, the Sanger Centre contributed large amounts of sequence, and also maps. They were there from the beginning and contributed at each stage. They contributed to all the model organisms as well as the human sequence. They contributed technology, ideas, and know-how.

JR: In the initial stages of the project there was much debate over whether or not the project was "big science." There was a lot of argument back and forth, and it seems to me that many people who were involved in the project constantly asserted that it was not big science. Why did that label have such a negative connotation to it?

EJ: Because of where biology was coming from. Biology was a science where individual scientists could pursue research and make important contributions, just based on their own work. Biologists view themselves as fortunate compared to a field like physics, where you can't do an experiment without a huge team of people and very expensive equipment. There was concern that biology would become like physics, dependent on these large accelerators and other kinds of gizmos and huge teams of people working together in order to get anything done. In some ways they were right. There still is lots of work for individual investigators coming up with their own ideas to pursue, but certainly many of the questions at the forefront now require multidisciplinary teams of people and significant equipment in order to do research.

So you can blame the Genome Project for that, but it's true even in areas of biology that are not directly related to genomics, such as structural biology and some of the systems biology. It's just where the field is going. We've answered the easy questions. We now have complex questions to answer that can best be addressed by large groups of people working together.

JR: Even while the multidisciplinary teams and the large centers were assuming a central role, were some of the more individualized projects still going on?

EJ: Yes. There were important contributions made by individual investigators; bacterial artificial chromosome comes to mind. That cloning vehicle was developed in an ordinary-sized lab, and some of the other technologies similarly came out of individual investigators pursuing their interests. It was not all centrally directed.

JR: Now that the sequence is on schedule for completion in 2003, what comes next?

EJ: Those steps have already started. There are all these other organisms to sequence, from mouse and rat to cows and dogs and monkeys and apes and—etcetera. So there's a lot more to be done now that scientists see how much information they can get out of the sequence, and they're just hungry for more. Another major direction is to study how sequence varies between individuals, and how that relates to biology. Just today I noticed an article in the paper. Apparently the Genome Institute has announced the award of grants to start the haplotype map, which will survey how much variation there is in the DNA between different groups of people, and create a database out of that which will then be the source of further research on how that links up with biology.

JR: How do you take something like the sequence or the maps, and then use those items to create a therapy or a product that can be used in medicine or pharmaceuticals?

EJ: In zillions of ways. One way is to use it to identify genes that are involved in whatever disease you're studying. Then you figure out what that gene is doing and try to intervene with some kind of drug to fix whatever problem is being created by the mutation. Having the whole genome just makes it easier to try and identify these genes that are involved in whatever disturbance is causing the disease. Classically, gene mapping involves studying inheritance in families and identifying a region of the genome in which there seems to be a difference, and then zeroing in on the gene and the mutation itself. Having the sequence of that region is such an immense time-saver, because it's already done. The map and the sequence already exist, so once you know where to look, you just look at the sequence and try to figure out which part of it might be involved in the disease.

Another approach is to build chips with bits of all the likely genes—or all the genes if you have enough chips—so that you can examine how the genes function on a large scale, and then compare their function, for example, in cancer tissue and in normal tissue, and see which genes are turned on or off in the cancer cell. Based on that, you can develop therapies that will try to correct those differences. There are just myriad ways that people use this information.

JR: Do you think the benefits of the sequence were oversold at all by the media and the more optimistic scientists? There were some who said, "This is the book of man, the holy grail of humanity," and there were others who said, "It's just another tool to use in research." Where do you think the truth falls in between those two extremes?

EJ: Well, it is the book of our life. All the genetic information that we have is in there, and just knowing that you have the whole set is a big step forward. Where the difficulty with prediction comes is how quickly are we going to see some of these benefits, and that remains unknown. It could be a few years; it could be many years before we see a significant impact on medical practice. I don't think anybody knows. That's where I think caution is in order, as far as promises. I think the potential is enormous, but the time frame is unknown.

JR: You've been involved in genetic research since before it was even called molecular biology. Looking back on your career at NHGRI and before, how has the landscape of genetic and biomedical research changed? What stands out to you as being some of the greatest changes that have occurred in the research?

EJ: They are so vast it's impossible to cover that in a few simple sentences. [Laughter] It's really been a whole series of revolutions. When we celebrate the fifty-year anniversary of the double helix and the completion of the human sequence next April, I'm sure reams will be written about it, and I know NIH is planning to celebrate it.

It's really mind-boggling in a way. If you take a picture of a lab in the fifties and a lab today, there's no comparison. [Laughs] In the fifties you had a few petri dishes and Erlenmeyer flasks, a Bunsen burner, and an incubator. Now we have rooms full of sequencing machines, robots, and other gizmos. It's just a whole different world, and I think different kinds of people are going to be attracted to the field now than were then.

JR: How important would you say the Genome Project has been in bringing about these changes?

EJ: I think it's a very important landmark. Maybe, in terms of changing the way biologists think and the way they do biology, it may be as significant as the discovery of the double helix. It's not as discrete an event. It's more a period of a decade or so where all these developments took place that changed the way we do things.

JR: Was there anything else that you wanted to add, anything that you think is important about the project that we haven't covered or that warrants more discussion?

EJ: Not that I can think of right now. [Laughter] We seem to have gone from one end to the other. I thought that we were going to focus mostly on the early period, so I hope you have what you need on that part.

JR: Most definitely. For being concerned about remembering, the level of detail that you've brought out in these interviews is phenomenal.

End of Interview #2

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[1] Per discussions with Dr. Jordan subsequent to the interview, the editor of *Science* has backed down and said in the February 14, 2003, issue that he will accept community standards recently promulgated by the National Academy of Sciences [NAS].